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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
BETH ANNE PIPER
APPLICATION NO: 09/460,920
FILED: DECEMBER 14, 1999
FOR: METHOD FOR TREATING DIABETES

Art Unit: 1614
Examiner: R. Cook

Assistant Commissioner for Patents
Washington, D.C. 20231

DECLARATION OF BURTON RODNEY IN SUPPORT OF DECLARATION OF PRIOR INVENTION OF BETH ANNE PIPER TO OVERCOME CITED U.S. PATENT NO. 6,303,146 (37 C.F.R. § 1.131)

To the Commissioner of Patents and Trademarks:

1. This Declaration is submitted in support of the Declaration of Prior Invention in the United States of Beth Anne Piper to Overcome Cited U.S. Patent No. 6,303,146 (37 C.F.R. § 1.131).

2. I, Burton Rodney, declare as follows:

3. I was employed as a full time patent attorney for Bristol-Myers Squibb Company and its predecessors from March, 1972 to April, 2000.

4. From October, 1999 to December 14, 1999 I drafted and filed a patent application covering the use of a low dose metformin/glyburide combination in the first-line treatment of diabetes.

5. Beth Anne Piper is the inventor of the use of a low dose metformin/glyburide combination in the first-line treatment of diabetes, a description of her conception of which is set out in an e-mail to me dated August 3, 1999 (identified as ATTACHMENT 1).

6. The actual date of conception of Beth Anne Piper's invention as claimed in the subject application was prior to July 15, 1998 as set out in Paragraph 6 of her Declaration of Prior Invention, which accompanies this Declaration.

7. The drafting of the subject application from October, 1999 to its filing less than 2.5 months later on December 14, 1999 is evidence of due diligence in the constructive reduction to practice of the invention claimed in the subject application.

Further Declarant sayeth not.

Burton Rodney

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000
(609) 252-4336

Date: January 23, 2003

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of application Serial No. 09/460,920 or any patent issued thereon.

Burton Rodney

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P.O. Box 4000
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Date: January 23, 2003

Subject: fixed combo met/gly
Date: Tue, 03 Aug 1999 09:46:54 -0400
From: "Beth A Piper" <piperb@bms.com>
Organization: Bristol-Myers Squibb
To: Burton Rodney <burton.rodney@bms.com>

Bud -

The fixed combo started out as a line extension for glucophage. Traditionally with diabetes therapies, combination therapy has only been indicated for second line use, after a monotherapy has been found to be inadequate or no longer controlling a patiet's blood sugar.

The concept of a fixed combination metformin/glyburide is not novel, it is marketed in 6-12 countries by various manufacturers. Both glyburide and metformin are older than I am but there is little to no data available on fixed combination use, I actually could only find two studies. the dosing is typically 400-500 mg of metformin with 2.5-5 mg of glyburide/glibenclimide or some other sulfonylurea.

When BMS approached the FDA about doing a fixed combination for second line therapy (with a 500/2.5 mg and 500/5 mg), the FDA replied that they wanted a firstline therapy trial as well. As it would be a single entity that might get used as first line or 'monotherapy' they wanted to know it would be safe in a different patient population or the population that did not yet require combination therapy for glycemic control. Approval depended upon safety trends as firstline therpy.

Not only was fixed combinaiton data hard to find but there was no data on combination therapy available as firstline treatment. From clinical experience I knew the planned dosing was too high for first line use and that we would see too much hypoglycemia compared to monotherapy. We then halved the 500/2.5 to get a 250/1.25 mg tablet strength. I knew it would work for glucose lowering and should be safe but didn't know how it would compare to monotherapy.

We couldn't have asked for better results. We beat placebo but were also statistically better than both glyburide monotherapy and metformin monotherapy with respect to glycemic efficacy. We have postive safety trends that the FDA was interested in, we are doing ad-hoc ananalysis in the ISS for both hypoglycemia and GI SE, We also got unexpected data that suggests that metformin has a postive or glucose sensitiziing effect on the pancreas. It is getting late I'll give you the deatils later.

Beth

Read and Understood
R.O. Parker August 3, 1999

SE = side effects

ATTACHMENT 1